(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 November 2004 (18.11.2004)

PCT

(10) International Publication Number
WO 2004/099377 A3

(51) International Patent Classification[7]: C12N 15/00, A61K 48/00

(21) International Application Number: PCT/US2004/013487

(22) International Filing Date: 30 April 2004 (30.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/467,171 1 May 2003 (01.05.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
24 February 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AN AUTOLOGOUS UPREGULATION MECHANISM ALLOWING OPTIMIZED CELL TYPE-SPECIFIC AND REGULATED GENE EXPRESSION CELLS

(57) Abstract: The present invention provides methods for high level, regulated transgene transcription that is restricted to cell populations of specific types. The process is designed to work with any inducible expression regulation systems, adapting them to a tissue-specific expression pattern while simultaneously delivering maximal achievable expression levels. In particular, the invention utilizes hybrid promoters that contain the DNA elements for both cell type-specific and regulated transcription. By placing the gene of the transcriptional activation factor (TAF) under the control of this tissue-specific/drug-regulated (TSDR) promoter, this invention achieves high expression levels of TAF in specific target cells by first initiating TAF expression using cell-type specific transcription elements, and subsequently amplifying transcriptional activity by establishing an autoregulatory positive feedback loop. In non-target cells, cell type-specific elements of the TSDR promoter will be inactive, the TAF expression will not be initiated, and auto-regulation will not occur. For cell type-specifc promoters with leaky low-level activity in non-target cells, a variation of this system has been developed which combines autologous upregulation of TAF with the expression of cross-competing transcriptional silencers (TSi) to achieve a type of eukaryotic "gene switch" - either shutting off transgene and TAF expression completely or promoting maximal expression levels.

WO 2004/099377 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/13487

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12N 15/00; A61K 48/00
US CL : 435/320.1, 514/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/320.1, 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/30799 A1 (RESEARCH DEVELOPMENT FOUNDATION) 03 May 2001 (03.05.2001), pages 7-8, 21-25 and 36-42.	1-4, 12-22, 28-32, 38-53
A	TANG et al. Vigilant vectors: adeno-associated virus witha biosensor to switch on amplified therapeutic genes in specific tissues in life-threatening diseases. Methods. 2002, Volume 28, pages 259-266, especially pages 259, 261 and 262.	1, 5-11, 14, 21, 23-27
A	QIAO et al. Tumor-specific transcriptional targeting of suicide gene therapy. Gene Therapy. 2002, Volume 9, pages 168-175, especially pages 168-169.	1, 5-11, 14-17, 21, 23-27, 31, 33-37, 41-25
A	SMITH-ARICA et al. Switching on and off transgene expression within lactotrophis cells in the anterior pituitary gland in vivo. Endocrinology. 2001, Volume 142, No. 6, pages 2521-2532, especially pages 2521, 2522 and 2524.	1, 5-12, 14-17, 21, 23-28, 31, 33-38, 40-45

☐ Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search
25 October 2004 (25.10.2004)

Date of mailing of the international search report
15 DEC 2004

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Form PCT/ISA/210 (second sheet) (January 2004)

Continuation of B. FIELDS SEARCHED Item 3:
EAST, MEDLINE, BIOSIS, EMBASE
search terms: vector, tissue specific, gene therapy, transcriptional activating factor (TAF), tissue specific regulatory element (TSRE), transcriptional silencer